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EDITORIAL

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Controversies in Diabetes in 2013 – a Brief Update

Kontrowersje w leczeniu cukrzycy w 2013 roku – krótkie podsumowanie

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract
Incidence of diabetes is increasing worldwide at an alarming rate. Therefore, a proper understanding of the mechanisms and efficient treatment of the disease is becoming increasingly important. The article briefly describes controversies in type 1 diabetes (T1DM) pathogenesis and diagnosis (genetic background, accelerator hypothesis, new autoantibodies, new information on LADA – latent autoimmune diabetes in adults, and the role of TRAIL – tumor necrosis factor-related apoptosis-inducing ligand) and treatment (how to deal with fluctuations of blood glucose concentrations and the occurrence of hypoglycemia, the role of healthy lifestyle, especially physical exercise, and a proper diet, treatment of insulin resistance and the challenges in detecting diabetic neuropathy). Moreover, issues in the pathogenesis of macrovascular complications in type 2 diabetes (T2DM) are considered (novel risk factors – vascular hyperglycemic memory, hypoglycemia, altered profile of microRNAs expression, impaired function of vascular progenitor cells, altered fibrin clot properties and iron-induced blood coagulation). Modern treatment of T2DM, based on lifestyle intervention and antidiabetic drugs, is full of controversies and it seems that over time the number of uncertainties is constantly increasing. Recent trials have reported disappointing results in lifestyle intervention (LOOK-AHEAD) and antihyperglycemic treatment (ACCORD, SAVOR-TIMI 53, EXAMINE, concerns about sulfonylureas safety). Moreover, there are considerable deviations from treatment targets that are recommended by the guidelines (blood glucose, hypertension, blood lipids) in real-life clinical practice in patients at different stages of the disease development. It seems that beneficial modification of the natural history of diabetes is unlikely in the foreseeable future unless we are able to obtain a more in-depth understanding of the pathomechanisms of the disease **(Adv Clin Exp Med 2013, 22, 6, 777–784).**

Key words: type 1 diabetes, type 2 diabetes, autoimmune diabetes, cardiovascular complications of diabetes.

Streszczenie
Częstość występowania cukrzycy na świecie zwiększa się bardzo szybko. Dlatego coraz ważniejsze staje się odpowiednie zrozumienie mechanizmów i skuteczne leczenie tej choroby. W artykule w skrócie opisano kontrowersje w poglądach na patogenezę i diagnostykę cukrzycy typu 1 (podłoże genetyczne, hipoteza akceleratora, nowe przeciwciała, nowa wiedza o LADA – utajonej autoimmunologicznej cukrzycy u dorosłych i rola TRAIL – związanego z czynnikiem martwicy nowotworu ligandu wywołującego apoptozę) oraz leczenie (postępowanie z wahaniami stężenia glukozy we krwi, zapobieganie występowaniu hipoglikemii, rola zdrowego stylu życia, zwłaszcza aktywności fizycznej i odpowiedniej diety, leczenie insulinooporności, wykrywanie neuropatii cukrzycowej). Omówiono ponadto zagadnienia patogenezy powikłań makronaczyniowych cukrzycy typu 2 (nowe czynniki ryzyka – metaboliczna pamięć naczyniowa, hipoglikemia, zmiany profilu ekspresji mikroRNA, zaburzenia czynności naczyniowych komórek progenitorowych, zmiany właściwości skrzepu fibrynowego, zaburzenia krzepnięcia krwi wywołanego żelazem). Nowoczesne leczenie cukrzycy typu 2 z uwzględnieniem zmian stylu życia i stosowaniem leków przeciwcukrzycowych jest nadal przedmiotem kontrowersji i wydaje się, że liczba wątpliwości nadal wzrasta. Ostatnie badania dotyczące modyfikacji stylu życia (LOOK-AHEAD) i leków przeciwcukrzycowych (ACCORD, SAVOR-TIMI 53, EXAMINE, zastrzeżenia co do bezpieczeństwa pochodnych sulfonylomocznika) nie przyniosły oczekiwanych wyników dotyczących poprawy rokowania sercowo-naczyniowego. Co więcej, w codziennej praktyce klinicznej występują istotne różnice między osiąganymi celami terapeutycznymi a zaleceniami do praktyki klinicznej

(stężenie glukozy we krwi, ciśnienie tętnicze, stężenie lipidów we krwi) we wszystkich stadiach rozwoju choroby. Wydaje się, że osiągnięcie korzystnej modyfikacji przebiegu klinicznego u chorych na cukrzycę jest mało prawdopodobne, jeżeli nie uda się bardziej szczegółowo poznać patomechanizmów choroby i jej powikłań **(Adv Clin Exp Med 2013, 22, 6, 777–784).**

Słowa kluczowe: cukrzyca typu 1, cukrzyca typu 2, cukrzyca o podłożu autoimmunologicznym, powikłania sercowo-naczyniowe cukrzycy.

Controversies in the Pathogenesis and Diagnosis of Type 1 Diabetes in Adults

Type 1 diabetes (T1DM) independent of age is an autoimmune disease with genetic background. HLA genes represent almost 50% of the familial risk of T1DM. Certain alleles of the HLA region, such as the HLA class II DR and DQ alleles, are mainly present in specific association with each other, a phenomenon known as linkage disequilibrium. The genotype that confers the highest risk of T1DM is the heterozygosity of the two high-risk HLA class II haplotypes: DR3 – DQ2 (DRB1* 03 – – DQA1* 0501 – B1* 0201) and DR4 – DQ8 (DRB1* 04 – DQA1* 0301 – B1* 0302). One or both of these haplotypes were found in more than 95% of people with T1DM younger than 30 years but also in approximately 40–50% of the general population. Using a candidate gene approach, several other non-HLA genes were found to be associated with increased risk of T1DM. These include genes encoding: insulin (INS), lymphocytic protein tyrosine phosphatase (PTPN22), the alpha chain of the IL-2 receptor (IL2R) and others mainly related to a specific and non-specific inflammatory response [1]. Recently, the relationship between IL-6 gene-174 G/C polymorphism and risk of T1DM has been intensively studied, but the results have been inconsistent. A meta-analysis of more than 18.000 subjects has suggested a lack of association between IL-6 gene-174 G/C polymorphism and the risk of T1DM [2].

The pathomechanism of T1DM includes 2 distinct stages in genetically susceptible individuals. The 1st is triggering of an autoimmune reaction resulting in autoantibodies against specific islet cells auto-antigens associated with gradual beta cell killing. The 2nd is loss of beta-cell secretory function manifested in infancy by the loss of 1st phase of insulin release and finally absolute deficiency of insulin. According to the accelerator hypothesis, the increased rate of beta-cell apoptosis and insulin resistance modulate the timing of clinical onset and subsequent course of autoimmune diabetes. However, the autoimmune process is thought to be the main accelerator of beta-cell destruction both before and after onset of T1DM [3].

Diagnosis of T1DM becomes increasingly difficult to distinguish from other types of diabetes after about 30–35 years of age. The term LADA (latent autoimmune diabetes in adults) was introduced to describe this subgroup of adult phenotypic type 2 diabetes but positive for an autoantibody to glutamine acid decarboxylase (GAD) [4]. LADA is a slowly progressive form of autoimmune disease causing diabetes and is characterized by the presence of serum autoantibodies to pancreatic antigens.

We have previously shown that a patient's age at autoimmune diabetes onset does not determine the clinical and biochemical presentation at diagnosis. The severity of the autoimmune process is reflected by the number of anti-islet cell antibodies. Patients with multiple autoantibodies seem to be at higher risk of having more pronounced destruction of β-cells and insulin deficiency. The IA-2A positivity was equally frequent in younger and older patients, and for the group of patients it was the only anti-islet antibody detected. These results of our previous study definitely highlight the potential importance of IA-2A in screening for autoimmunity in newly diagnosed adult diabetic patients [4].

Recently, a new autoantibody has been revealed to be connected with autoimmune diabetes. Zinc transporter 8 (ZnT8) autoantibodies are believed to be part of the autoimmune process. The gene that is responsible for coding ZnT8 is named SCL30A8 and is localized on chromosome 8q24.11 [5]. ZnT8A are present in both juvenile-onset T1DM and in adult onset autoimmune diabetes. It was noticed that the number of autoantibody-negative patients was lower when a ZnT8 assay aside from other measurements was performed. Lampasona et al. revealed that the presence of ZnT8A was connected with younger age and high GADA titer among adult-onset autoimmune diabetes [6].

TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) is a transmembrane protein expressed on most cells that regulates homeostasis of the immune system and inflammatory reaction [7]. There is emerging evidence to support an association between TRAIL and diabetes. The main mechanism of beta-cell destruction is apoptosis. *T* cell induced death seems to be the main

source of TRAIL in the pancreas in T1DM. An association between TRAIL and autoimmune diabetes has been noticed, but their role is controversial because both apoptotic and protective roles have been described [8]. It is not surprising that a relationship between TRAIL and insulin resistance, obesity and cancer has been noted. TRAIL reflects the inflammatory process that plays a key role in the listed pathology.

Controversies in the Management of Type 1 Diabetes

The therapeutic goals in patients with T1DM include prevention of the chronic and acute complications of diabetes while maintaining good quality of life. Established risk factors for microvascular complications in T1DMi include chronic hyperglycemia, hypertension and dyslipidemia. Maintaining good metabolic control is effective in decreasing the risk of chronic complications, but new approaches are needed to control the residual risk.

Measurement of glycation products, such as glycated hemoglobin, fructosamine and glycated albumin, reflect the average blood glucose concentration from a time interval preceding the assay, but do not account for the fluctuations of blood glucose concentrations and the occurrence of hypoglycemia [9]. This also applies to the novel techniques of noninvasive measurement of skin autofluorescence to detect advanced glycation end products (AGEs) accumulation in the skin that seems to reflect glycemic control over periods of time much longer than HbA1c assay [10]. Evidence from preclinical studies shows that fluctuating glucose levels may increase oxidative stress and have an even more deleterious effect than constantly high glucose exposure [11]. One may therefore hypothesize that control of daily blood glucose fluctuations, in addition to management of chronic hyperglycemia (as measured by HbA1c) in diabetic patients, may protect against micro- and macrovascular disease.

The relationship between glycemic variability and the development of chronic complications is controversial and long-term observations and standardized methods of measurement of glycemic variability are needed to clarify this issue [12]. High glycemic variability is also associated with severe hypoglycemia in patients with T1DM [13]. Despite the lack of definitive evidence on the influence of glycemic variability on hard endpoints other than hypoglycemia, contemporary and emerging treatment options help reduce fluctuations of glycemic. As a consequence, increased incidence of hypoglycemia is not an inevitable consequence of the intensification of glycemic control. In patients on intensive insulin therapy using multiple insulin injections, switching to long acting insulin analogue may help reduce the events of hypoglycemia, particularly during the night [14]. New methods of controlling glycemic variability range from the use of continuous glucose monitoring systems (CGMS), with or without the possibility to discontinue insulin delivery in case of hypoglycemia, to the increasingly tested systems with automatic adjustment of insulin delivery depending on glycemic (closed loop insulin delivery) [15]. Attempts are also being made to use both insulin and glucagon (dual hormone therapy) to better approximate the physiologic mechanism of glycemic control [16]. According to a recent meta-analysis [17], the use of CGMS in patients with T1DM treated with intensive insulin therapy (multiple daily insulin injections or continuous subcutaneous insulin infusion) was associated with a small (0.3%) yet significant reduction in HbA1c, with simultaneously reduced exposure to hypoglycemia. It should be underlined, however, that according to the clinical guidelines and common practice, the use of CGM requires close involvement of the patient in the treatment process and the efficacy of CGM largely depends on patient selection, education and close follow-up [18].

In T1DM, the presence and degree of residual insulin secretion is associated with better metabolic control reflected by a decrease in the episodes of hyperglycemia, diabetic ketoacidosis (DKA) and also hypoglycemia. Clinical remission of T1DM is a phase of the disease when insulin secretion is present to a significant degree, sometimes comparable to non-diabetic individuals. It is unknown if the presence or duration of partial remission may be associated with sustained long-term residual insulin secretion and a decrease in the risk of chronic complications. However, the partial remission phase serves as a model to test how lifestyle or pharmacological interventions are effective in maintaining insulin secretion in patients with type 1 diabetes. For instance, it was shown that cigarette smoking is associated with a shortening of partial remission [19].

Evidence is accumulating that physical activity in many ways positively influences the course of T1DM. Sedentary lifestyle has been associated with poor glycemic control in young patients with T1DM [20]. Some studies have demonstrated an improvement in glycated hemoglobin (HbA1c) after physical activity [21]. The influence of physical activity on glycemic control may also depend on

the form of training. The results of a recent meta-analysis demonstrate that only regular aerobic exercise programs significantly improved acute and chronic glycemic control [22]. Moreover, the composition of training sessions may also have a role in maintaining metabolic control, as the addition of brief bouts of high-intensity exercise to aerobic exercise was found to decrease the risk of late hypoglycemic episodes occurring after training [22]. Of note, in the studies that demonstrated the positive effect of exercise on glycemic control, the decrease in HbA1c was not associated with a significant increase in the frequency of hypoglycemia. An increase in physical activity is commonly associated with decreased insulin requirement, which may be explained mainly by an increased insulin-independent glucose uptake by myocytes and increased peripheral insulin sensitivity [23]. Available evidence suggests the positive influence of physical activity on beta-cell function in patients with T2DM, overweight non-diabetic subjects, and NOD mice and a pilot trial has been designed recently to test this effect in adults with newly diagnosed T1DM [24].

The effect of physical activity on the hard endpoints in the course of T1DM appears to be beneficial, although the evidence on this is based mainly on retrospective studies, such as the FinnDiane study [25]. Large prospective studies are needed to confirm this effect in patients with type 1 diabetes. Not only leisure-time physical activity, but also professional practice of competitive sports appears to be safe and beneficial for educated patients with well-controlled type 1 diabetes.

Insulin resistance is common in T1DM and is associated with an increased risk of its chronic complications [26]. In patients with T1DM, physical activity may decrease oxidative stress and reverse endothelial dysfunction [26], both of these effects may result in increased insulin sensitivity. Among other lifestyle components, short sleep duration was found to be associated with insulin resistance in patients with T1DM [27]. Also, cigarette smoking, triggering hormonal responses that are counter-regulatory to insulin, decreases insulin sensitivity [28].

Some trials addressed the efficacy of metformin, the drug registered in type 2 diabetes that mainly decreases hepatic insulin resistance, as an add-on treatment in T1DM. In a recent meta-analysis, metformin use was associated with a statistically and clinically significant reduction in HbA1c (0.6–0.9%), along with reduced insulin requirement, decreased body weight and serum total cholesterol concentration. Moreover, the metformin treatment appeared to be safe, with an increased prevalence of hypoglycemia as the main adverse event [29].

In the current approach, the diet recommended to the majority of patients with T1DM does not differ from a healthy diet suggested for the non-diabetic population. Restrictions on the consistent day-to-day carbohydrate content of meals is an important consideration where premixed insulin or fixed basal-bolus treatment are used. Patients who are well educated and adjust insulin doses to the carbohydrate content of the meals do not need such restrictions to achieve adequate control of glycemic. The use of the glycemic index (GI) in food choices may be beneficial in maintaining normoglycemia and is increasingly popular in T1DM patients, but they must be advised not to increase saturated fat intake when introducing the low-GI diet. Apart from its pro-atherogenic effect, in the DCCT cohort, increased fat intake was associated with worse glycemic control independent of exercise and BMI [30]. Despite the fact that products with a high glycemic index are not strictly forbidden for patients with T1DM, especially those using flexible intensive insulin treatment, a rapid rise of postprandial glycemia following these meals is difficult to control even with rapid-acting insulin analogues. The other cause of increased fat intake in some patients with T1DM may be low-carbohydrate nutrition used in an effort to minimize the need for insulin injections or to lose weight. As a consequence, many people with T1DM consume a diet higher in fat and saturated fat than members of the general population [31]. The frequent intake of high-GI snacks by children and adolescents has led to obesity, dyslipidemia and poor glycemic control [32]. Interestingly, frequent consumption of diet beverages is also associated with poor metabolic control of T1DM, similarly to the consumption of sweetened beverages, possibly being a marker of an unhealthy diet pattern [32]. Many young people with T1DM present a lifestyle associated with low attention to dietary choices and frequent consumption of fast-food. Apart from other negative effects, this diet is usually associated with a very high intake of food rich in trans unsaturated fatty acids (from hydrogenated vegetable oils) and food additives.

Among the diagnostic strategies of detecting the chronic complications of type 1 diabetes, the most challenging one is early detection of diabetic neuropathy, since the sensitivity of the widely-used tests is low when compared with the methods of screening for diabetic retinopathy or diabetic kidney disease. The diagnostic procedures currently used for research purposes, including the measurement of intraepidermal nerve fiber density [33] and measurement of nerve conduction velocity [34], are invasive and complex, which limits their widespread use. Examining the degree of retinal degeneration using optical coherence tomography (OCT) enables

measurement of retinal thickness with identification of individual retinal layers, revealing manifestations of both neuropathy and retinopathy [35]. Novel noninvasive tools for diabetic neuropathy screening may check sudomotor dysfunction, which indirectly reveals small fiber dysfunction, with high sensitivity and modest specificity [36].

Controversies in the Pathogenesis of Macrovascular Complications in Type 2 Diabetes

Besides ageing of the population, lifestyle changes and lower physical activity leading to a higher prevalence of obesity are responsible for the fact that the incidence of type 2 diabetes (T2DM) is increasing worldwide at an alarming rate [37]. In a recent study, it was demonstrated that 16.3% of the Polish population is affected by various carbohydrate metabolism disorders (6.8% of people had diabetes and 9.5% impaired fasting glucose) [38]. The vascular complications of T2DM caused by atherosclerosis are the most serious manifestations of the disease and are largely responsible for decreased life expectancy in those patients [39]. Although epidemiological evidence clearly suggests that diabetic hyperglycemia is a major risk factor for macrovascular complications, recent clinical trials have clearly demonstrated that intensive glucose lowering treatment shows limited benefits on the cardiovascular (CV) system and all cause mortality in patients with T2DM and CV disease [39]. Therefore, to improve the therapeutic approach, it is necessary to go from bedside-to-bench again to better understand the pathomechanisms of macrovascular complications in T2DM.

While the vascular complications of diabetes are mainly due to insulin resistance and hyperglycemia leading to oxidative stress and clustering with arterial hypertension, dyslipidemia as well as genetic susceptibility, novel risk factors have recently come under investigation [37]. They include, among others, vascular hyperglycemic memory, the pathophysiological consequences of hypoglycemia, an altered profile of microRNAs expression and impaired function of vascular progenitor cells [39]. Moreover, individuals with T2DM are also at increased risk of thrombotic coronary events, which are driven by an increase in platelet activation, enhanced thrombin generation and altered fibrin clot properties [40].

Recently, a novel pathway of blood coagulation was described which might have important implications for T2DM patients [41]. It was demonstrated that fibrinogen, besides being a precursor to fibrin, can be converted into an insoluble polymer by hydroxyl radicals which are generated with the involvement of trivalent ferric ions, without the participation of any redox agent [41]. Therefore, the role of iron overload might be a novel pathomechanism for the pro-thrombotic state and cardiovascular complications observed in diabetes and a new target for therapy.

Coagulation in diabetic patients can also be affected by even mild hypoglycemia. Very recently, it was shown that even a single episode of hypoglycemia induces pro-thrombotic changes in the fibrin network and aggravates subclinical inflammation, and these effects are sustained for at least 1 week [42].

It is becoming clear that future treatment paradigms for T2DM patients will need to encompass a broader spectrum of pathophysiological determinants than previously expected.

Controversies in the Management of Type 2 Diabetes

Modern treatment of T2DM, based on lifestyle intervention and antidiabetic drugs, is full of controversies and it seems that over time the number of uncertainties constantly increases. Similarly to T1DM, recommendations for lifestyle modification through healthy diet and increased physical activity have been the foundation on which all additional T2DM therapies should rest. Unfortunately, recently a large, prospective and randomized LOOK-AHEAD Trial on lifestyle intervention in obese T2DM patients was stopped early after a median follow-up of almost 10 years, when interim analyses suggested neutral effects on cardiovascular outcomes, a finding that was consistent across all reported subgroups [43].

In 2013, there is an ever-increasing range of antihyperglycemic options for the treatment of patients with T2DM [44]. Although all of the guidelines and regulatory agencies consider lowering blood glucose and glycated hemoglobin in T2DM an approvable end point, very intensive glycemic control might be associated with increased mortality in those patients [44, 45]. There are also recurring controversies regarding higher cancer risk in patients treated with some hypoglycemic medications, although the majority of the available studies assessing that effect have significant limitations [46]. On the other hand, better glycemic control delays the onset and progression of microvascular complications [39]. Therefore the choice

of optimal drugs and treatment algorithms becomes a major controversy [44]. Unfortunately, direct and fair comparisons between drugs and regimens are lacking and the clinician is left to decide among agents with different safety and burden profiles [44]. One such controversy concerns sulfonylurea, which is, in some countries (including Poland), a major and widely accessible antidiabetic drug. In a very recent retrospective study of 92.498 patients with T2DM, first-line therapy with sulfonylurea increased the risk for all-cause mortality by 58% when compared with metformin [47]. Recently, sulfonylurea was also responsible for a significant increase in hypoglycemia rates in major clinical studies involving dipeptidyl peptidase 4 (DPP-4) inhibitors and this might be partly responsible for the neutral effect of that newer generation of antidiabetic drugs on CV outcomes [45].

Therefore, it seems that glycemic control is not the only or the most important goal for most patients with T2DM and special care should be taken to treat patients' concomitant risk factors for macrovascular complications, especially hypertension and hyperlipidemia. Unfortunately, considerable deviations from the treatment targets that are recommended by the guidelines exist in real-life clinical practice among patients at different stages of the disease development. In newly diagnosed T2DM patients in an ARETAEUS study, only 1.4% of the patients met all their treatment goals (HbA1c, blood pressure, and lipid levels), and as much as 51% did not meet any of the targets [48]. In a recent OPTIMO study performed in specialty outpatient clinics in Poland, it was demonstrated that the majority of referred patients do not meet the treatment goals recommended by the guidelines (67% for hyperlipidemia and 49% for hypertension) [49]. This might be due to underuse of cardiovascular drugs in T2DM patients, despite their proven efficacy. In the Kardia-Pol registry in primary care, only 70% of T2DM patients received angiotensin-blocking agents and 64% were treated with statins, despite the high prevalence of the above-mentioned risk factors [50]. Assuming that adherence to the current clinical practice guidelines is beneficial for patients, it is crucial that both practitioners and patients have increased awareness of these guidelines and of the ways to achieve and maintain treatment goals [48].

Conclusions

The most effective prevention of diabetic complications would likely be to safely achieve perfect metabolic control and to successfully treat other risk factors for micro- and macrovascular complications. It seems that achievement of this goal is unlikely in the foreseeable future.

As a wealth of mechanistic information is accumulating regarding the pathophysiology of diabetes and its complications, it is becoming clear that without proper understanding of those complex mechanisms, the discovery of beneficial treatment regimens for diabetic patients will not be possible.

References

[1] **Okruszko A, Szepietowska B, Wawrusiewicz-Kurylonek N, Gorska M, Kretowski A, Szelachowska M:** HLA-DR, HLA-DQB1 and PTPN22 gene polymorphism: association with age at onset for autoimmune diabetes. Arch Med Sci 2012, 8, 874–878.

[2] **Yan-Wei Yin, Qian-Qian Sun, Bei-Bei Zhang, Ai-Min Hu, Qi Wang, Hong-Li Liu, Zhi-Zhen Hou, Yi-Hua Zeng, Rui-Jia Xu, Long-Bao Shi:** The lack of association between interleukin-6 gene-174 G/C polymorphism and the risk of type 1 diabetes mellitus: A meta-analysis of 18 152 subjects. Gene 515 2013, 461–465.

[3] **Dabelea D, Mayer-Davis EJ, Andrews JS, Dolan LM, Pihoker C, Hamman RF, Greenbaum C, Marcovina S, Fujimoto W, Linder B, Imperatore G, D'Agostino R Jr:** Clinical evolution of beta cell function in youth with diabetes: the SEARCH for Diabetes in Youth study. Diabetologia 2012, 55, 3359–3368.

[4] **Paschke A, Grzelka A, Zawada A, Zozulińska-Ziółkiewicz D:** Clinical characteristics and autoantibody pattern in newly diagnosed adult-onset autoimmune diabetes. Pol Arch Med Wewn 2013, 123, 401–408.

[5] **Wenzlau JM, Moua O, Sarkar SA, Yu L, Rewers M, Eisenbarth GS, Davidson HW, Hutton JC:** SlC30A8 is a major target of humoral autoimmunity in type 1 diabetes and a predictive marker in pre-diabetes. Ann N Y Acad Sci 2008, 1150, 256–259.

[6] **Lampasona V, Petrone A, Tiberti C, Capizzi M, Spoletini M, di Pietro S, Songini M, Bonicchio S, Giorgino F, Bonifacio E, Bosi E, Buzzetti R:** Zinc transporter 8 antibodies complement GAD and IA-2 antibodies in the identification and characterization of adult-onset autoimmune diabetes: Non Insulin Requiring Autoimmune Diabetes (NIRAD) 4. Diabetes Care 2010, 33, 104–108.

[7] **Azahri NS, Kavurma MM:** Transcriptional regulation of tumour necrosis factor-related apoptosis-inducing ligand. Cell Mol Life Sci 2013, 70, 3617–3629.

[8] **Vaccarezza M, Delbello G, Zauli G:** A role of the TRAIL-TRAIL receptor system in the pathogenesis of diabetes. Acta Biomed 2007, 78, Suppl 1, 262–267.

[9] **Nathan DM, McGee P, Steffes MW, Lachin JM:** Relationship of Glycated Albumin to Blood Glucose and Glycated Hemoglobin (HbA1C) Values and to Retinopathy, Nephropathy and Cardiovascular Outcomes in the DCCT/ /EDIC Study Diabetes 2013.
[10] **Samborski P, Naskret D, Araszkiewicz A, Niedzwiecki P, Zozulinska-Ziolkiewicz D, Wierusz-Wysocka B:** Assessment of skin autofluorescence as a marker of advanced glycation end product accumulation in type 1 diabetes. Pol Arch Med Wewn 2011, 121, 67–72.
[11] **Picconi F, Di Flaviani A, Malandrucco I, Giordani I, Frontoni S:** Impact of glycemic variability on cardiovascular outcomes beyond glycated hemoglobin. Evidence and clinical perspectives. Nutr Metab Cardiovasc Dis 2012, 22, 691–696.
[12] **Picconi F, Di Flaviani A, Malandrucco I, Giordani I, Longo S, Frontoni S:** The need for identifying standardized indices for measuring glucose variability. J Diabetes Sci Technol 2012, 6, 218–219.
[13] **Kilpatrick ES, Rigby AS, Goode K, Atkin SL:** Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia 2007, 50, 2553–2561.
[14] **Szypowska A, Golicki D, Groele L, Pankowska E:** Long-acting insulin analogue detemir compared with NPH insulin in type 1 diabetes: a systematic review and meta-analysis. Pol Arch Med Wewn 2011, 121, 237–246.
[15] **Elleri D, Allen JM, Kumareswaran K, Leelarathna L, Nodale M, Caldwell K, Cheng P, Kollman C, Haidar A, Murphy HR, Wilinska ME, Acerini CL, Dunger DB, Hovorka R:** Closed-loop basal insulin delivery over 36 hours in adolescents with type 1 diabetes: randomized clinical trial. Diabetes Care 2013, 36, 838–844.
[16] **McCall AL, Farhy LS:** Treating type 1 diabetes: from strategies for insulin delivery to dual hormonal control. Minerva Endocrinol 2013, 38, 145–163.
[17] **Wojciechowski P, Rys P, Lipowska A, Gaweska M, Malecki MT:** Efficacy and safety comparison of continuous glucose monitoring and self-monitoring of blood glucose in type 1 diabetes: systematic review and meta-analysis. Pol Arch Med Wewn 2011, 121, 333–343.
[18] **Benhamou PY, Catargi B, Delenne B, Guerci B, Hanaire H, Jeandidier N, Leroy R, Meyer L, Penfornis A, Radermecker RP, Renard E, Baillot-Rudoni S, Riveline JP, Schaepelynck P, Sola-Gazagnes A, Sulmont V, Tubiana-Rufi N, Durain D, Mantovani I, Sola-Gazagnes A, Riveline JP:** Real-time continuous glucose monitoring (CGM) integrated into the treatment of type 1 diabetes: consensus of experts from SFD, EVADIAC and SFE. Diabetes Metab 2012, 38, Suppl 4, S67–83.
[19] **Scholin A, Nystrom L, Arnqvist H, Bolinder J, Björk E, Berne C, Karlsson FA:** Proinsulin/C-peptide ratio, glucagon and remission in new-onset Type 1 diabetes mellitus in young adults. Diabet Med 2011, 28, 156–161.
[20] **Pilacinski S, Adler AI, Zozulinska-Ziolkiewicz DA, Gawrecki A, Wierusz-Wysocka B:** Smoking and other factors associated with short-term partial remission of Type 1 diabetes in adults. Diabet Med 2012, 29, 464–469.
[21] **Galler A, Lindau M, Ernert A, Thalemann R, Raile K:** Associations between media consumption habits, physical activity, socioeconomic status, and glycemic control in children, adolescents, and young adults with type 1 diabetes. Diabetes Care 2011, 34, 2356–2359.
[22] **Tonoli C, Heyman E, Roelands B, Buyse L, Cheung SS, Berthoin S, Meeusen R:** Effects of different types of acute and chronic (training) exercise on glycaemic control in type 1 diabetes mellitus: a meta-analysis. Sports Med 2012, 42, 1059–1080.
[23] **Langfort J, Viese M, Ploug T, Dela F:** Time course of GLUT4 and AMPK protein expression in human skeletal muscle during one month of physical training. Scand J Med Sci Sports 2003, 13, 169–174.
[24] **Lascar N, Kennedy A, Jackson N, Daley A, Dowswell G, Thompson D, Stokes K, Greenfield S, Holder R, Andrews R, Narendran P:** Exercise to preserve beta cell function in recent-onset type 1 diabetes mellitus (EXTOD) – a study protocol for a pilot randomized controlled trial. Trials 2013, 14, 180.
[25] **Wadén J, Forsblom C, Thorn LM, Saraheimo M, Rosengård-Bärlund M, Heikkilä O, Lakka TA, Tikkanen H, Groop PH:** Physical activity and diabetes complications in patients with type 1 diabetes: The Finnish diabetic nephropathy (FinnDiane) study. Diabetes Care 2008, 31, 230–232.
[26] **Seeger JP, Thijssen DH, Noordam K, Cranen ME, Hopman MT, Nijhuis-van der Sanden MW:** Exercise training improves physical fitness and vascular function in children with type 1 diabetes. Diabetes Obes Metab 2011, 13, 382–384.
[27] **Donga E, van Dijk M, van Dijk JG, Biermasz NR, Lammers GJ, van Kralingen K, Hoogma RP, Corssmit EP, Romijn JA:** Partial sleep restriction decreases insulin sensitivity in type 1 diabetes. Diabetes Care 2010, 33, 1573–1577.
[28] **Seet RC, Loke WM, Khoo CM, Chew SE, Chong WL, Quek AM, Lim EC, Halliwell B:** Acute effects of cigarette smoking on insulin resistance and arterial stiffness in young adults. Atherosclerosis 2012, 224, 195–200.
[29] **Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR:** The use of metformin in type 1 diabetes: a systematic review of efficacy. Diabetologia 2010, 53, 809–820.
[30] **Delahanty LM, Nathan DM, Lachin JM, Hu FB, Cleary PA, Ziegler GK, Wylie-Rosett J, Wexler DJ:** Association of diet with glycated hemoglobin during intensive treatment of type 1 diabetes in the Diabetes Control and Complications Trial. Am J Clin Nutr 2009, 89, 518–524.
[31] **Snell-Bergeon JK, Chartier-Logan C, Maahs DM, Ogden LG, Hokanson JE, Kinney GL, Eckel RH, Ehrlich J, Rewers M:** Adults with type 1 diabetes eat a high-fat atherogenic diet that is associated with coronary artery calcium. Diabetologia 2009, 52, 801–809.
[32] **Bortsov AV, Liese AD, Bell RA, Dabelea D, D'Agostino RB Jr, Hamman RF, Klingensmith GJ, Lawrence JM, Maahs DM, McKeown R, Marcovina SM, Thomas J, Williams DE, Mayer-Davis EJ:** Sugar-sweetened and diet beverage consumption is associated with cardiovascular risk factor profile in youth with type 1 diabetes. Acta Diabetol 2011, 48, 275–282.

[33] **Sveen KA, Karimé B, Jørum E, Mellgren SI, Fagerland MW, Monnier VM, Dahl-Jørgensen K, Hanssen KF:** Small- and Large-Fiber Neuropathy After 40 Years of Type 1 Diabetes: Associations with glycemic control and advanced protein glycation: The Oslo Study. Diabetes Care 2013.
[34] **Hyllienmark L, Alstrand N, Jonsson B, Ludvigsson J, Cooray G, Wahlberg-Topp J:** Early Electrophysiological Abnormalities and Clinical Neuropathy: A prospective study in patients with type 1 diabetes. Diabetes Care 2013, 36, 3187–3194.
[35] **Araszkiewicz A, Zozulińska-Ziółkiewicz D, Meller M, Bernardczyk-Meller J, Piłaciński S, Rogowicz-Frontczak A, Naskręt D, Wierusz-Wysocka B:** Neurodegeneration of the retina in type 1 diabetic patients. Pol Arch Med Wewn 2012, 122, 464–470.
[36] **Ziegler D, Papanas N, Roden M:** Neuropad: evaluation of three cut-off points of sudomotor dysfunction for early detection of polyneuropathy in recently diagnosed diabetes. Diabet Med 2011, 28, 1412–1415.
[37] **Paneni F, Beckman JA, Creager MA, Cosentino F:** Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J 2013, 34, 2436–2443.
[38] **Polakowska M, Piotrowski W:** Incidence of diabetes in the Polish population: results of the Multicenter Polish Population Health Status Study – WOBASZ. Pol Arch Med Wewn 2011, 121, 156–163.
[39] **Rask-Madsen C, King GL:** Vascular complications of diabetes: mechanisms of injury and protective factors. Cell Metab 2013, 17, 20–33.
[40] **Undas A:** Acquired dysfibrinogenemia in atherosclerotic vascular disease. Pol Arch Med Wewn 2011, 121, 310–319.
[41] **Lipinski B, Pretorius E:** Novel pathway of iron-induced blood coagulation: implications for diabetes mellitus and its complications. Pol Arch Med Wewn 2012, 122, 115–122.
[42] **Chow EYK, Iqbal A, Phoenix F, Heller SR, Ajjan R:** Hypoglycaemia promotes thrombosis and inflammation for at least one week in patients with type 2 diabetes. Diabetologia 2013, 56 (Suppl 1), S243.
[43] Look AHEAD Research Group Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. N Engl J Med 2013, 369, 145–154.
[44] **Montori VM, Deming J, Shah ND:** How should clinicians and patients choose antihyperglycemic agents?: an evidence-based approach. Pol Arch Med Wewn 2011, 121, 208–212.
[45] **Hiatt WR, Kaul S, Smith RJ:** The Cardiovascular Safety of Diabetes Drugs – Insights from the Rosiglitazone Experience. N Engl J Med 2013, 369, 1285–1287.
[46] **Drzewoski J, Drozdowska A, Sliwińska A:** Do we have enough data to confirm the link between antidiabetic drug use and cancer development? Pol Arch Med Wewn 2011, 121, 81–87.
[47] **Jenkins-Jones S, Currie CJ, Mukherjee J, Morgan CI:** Association between first-line monotherapy with sulfonylurea versus metformin and risk of all-cause mortality. Diabetologia 2013, 56 (Suppl 1), S89.
[48] **Bała MM, Płaczkiewicz-Jankowska E, Topór-Mądry R, Leśniak W, Jaeschke R, Sieradzki J, Grzeszczak W, Banasiak W:** ARETAEUS Study Group. Is newly diagnosed type 2 diabetes treated according to the guidelines? Results of the Polish ARETAEUS1 study. Pol Arch Med Wewn 2011, 121, 7–17.
[49] **Jankowski M, Bała MM, Płaczkiewicz-Jankowska E, Topór-Mądry R, Mejza F, Jaeschke R, Sieradzki J, Gajewski P:** Specialty outpatient care of diabetic patients in Poland – are we far from treatment targets? Rationale, design, and preliminary results of the OPTIMO study. Pol Arch Med Wewn 2011, 121, 375–378.
[50] **Opolski G, Strojek K, Kurzelewski M, Ostrowski M, Rabczenko D:** Cardiovascular therapy, diagnostic procedures, and control of risk factors in patients with diabetes or coronary artery disease in Poland: the Kardia-Pol registry. Pol Arch Med Wewn 2012, 122, 413–421.

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